P. ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 December 1999 (01.12.99)	
International application No. PCT/GB99/01066	**Applicant's or agent's file reference** HL52257/001
International filing date (day/month/year) 07 April 1999 (07.04.99)	**Priority date** (day/month/year) 07 April 1998 (07.04.98)
Applicant ARMITAGE, William, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 October 1999 (18.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J.M. Vivet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

[redacted]ENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
HL52257/001		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 01066	07/04/1999	07/04/1998
Applicant		
UNIVERSITY OF BRISTOL et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   OCULAR IRRIGATING SOLUTION

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/GB 99/01066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 725 586 A (LINDSTROM ET AL.) 16 February 1988 (1988-02-16) column 1, line 10 - line 30 column 3, line 18 - line 36 column 4, line 8 - line 40 ---	1-12
X	EP 0 435 797 A (ANBEN) 3 July 1991 (1991-07-03) the whole document ---	1-3,5-12
X	FR 2 602 677 A (BLOMET) 19 February 1988 (1988-02-19) page 8; examples 2,3 ---	1-3
A	EP 0 778 021 A (TAISHO PHARMACEUTICAL CO. LTD) 11 June 1997 (1997-06-11) the whole document --- -/--	1-3,5-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/GB 99/01066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 064 320 A (WELSH NATIONAL SCHOOL OF MEDICINE) 17 June 1981 (1981-06-17) the whole document	1-12
A	DE 196 26 479 A (SCHRAGE) 8 January 1998 (1998-01-08) the whole document	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

tion on patent family members

International Application No
[redacted]T/GB 99/01066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4725586 A	16-02-1988	US 4696917 A	29-09-1987
		CA 2042152 A	14-11-1992
		EP 0232377 A	19-08-1987
		GB 2186798 A,B	26-08-1987
		JP 63500720 T	17-03-1988
		WO 8700753 A	12-02-1987
		US 4886786 A	12-12-1989
EP 435797 A	03-07-1991	FR 2656527 A	05-07-1991
		AT 112674 T	15-10-1994
		DE 69013315 D	17-11-1994
		DE 69013315 T	24-05-1995
		DK 435797 T	16-01-1995
		ES 2063950 T	16-01-1995
		US 5380537 A	10-01-1995
FR 2602677 A	19-02-1988	NONE	
EP 778021 A	11-06-1997	AU 3484895 A	29-03-1996
		CA 2199610 A	21-03-1996
		CN 1160346 A	24-09-1997
		WO 9608244 A	21-03-1996
		JP 8133968 A	28-05-1996
GB 2064320 A	17-06-1981	NONE	
DE 19626479 A	08-01-1998	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HL52257/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01066	07/04/1999	07/04/1998
International Patent Classification (IPC) or national classification and IPC A61K9/08		
Applicant UNIVERSITY OF BRISTOL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/10/1999	05.05.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Uhl. M Telephone No. +49 89 2399 8654

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01066

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-12 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11 as far as industrial applicability is concerned.

because:

☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 12 as far as novelty and inventive step is concerned are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claim 12 contains a reference to the description (here: examples). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here. Accordingly, there was no examination concerning novelty and inventive step for claim 12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claim 11 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Ad V.2 (Citations and Explanations)

D1 US 4 725 586 A 16 February 1988 (1988-02-16)
see in particular: col.1, l.10-30, col.3, l.18-36, col.4, l.8-40

D2 EP 0 435 797 A 3 July 1991 (1991-07-03)
see in particular: p.3, l.44-45, p.4, exemple, cl.1, cl.8

D3 FR 2 602 677 A 19 February 1988 (1988-02-19)
see in particular: p.8, ex.2 and 3

Novelty and inventive step (Art. 33 (2) and (3) PCT):

Ocular irrigation solutions comprising a bicarbonate source (concentration between 10 and 50 mmol) and an organic zwitterionic buffer (HEPES, Glycocoll) and its use in ophtalmic surgery is disclosed in the prior art. Subject matter of claims 1-10 (composition) and 11 (its use in surgery) is therefore not regarded to be novel over the prior art.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/08

A1

(11) International Publication Number: **WO 99/51204**

(43) International Publication Date: 14 October 1999 (14.10.99)

(21) International Application Number: PCT/GB99/01066

(22) International Filing Date: 7 April 1999 (07.04.99)

(30) Priority Data:
9807491.7 7 April 1998 (07.04.98) GB

07 Oct 00/30 mos

(71) Applicant *(for all designated States except US)*: UNIVERSITY OF BRISTOL [GB/GB]; Senate House, Tyndall Avenue, Bristol, Avon BS8 1TH (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ARMITAGE, William, John [GB/GB]; 34 Hutton Close, Westbury–on–Trim, Bristol, Avon BS9 3PT (GB). YAGOUBI, Mohamed, Ibrahim [LY/GB]; University of Bristol, Dept. of Opthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol, Avon BS1 2LX (GB).

(74) Agent: NASH, David, Allan; Haseltine Lake & Co., Imperial House, 15–19 Kingsway, London WC2B 6UD (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OCULAR IRRIGATING SOLUTION

(57) Abstract

There is disclosed an ocular irrigating solution for irrigating the eye during surgery comprising a source of bicarbonate ions an d a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

OCULAR IRRIGATING SOLUTION

This invention relates to aqueous solutions for use in surgical procedures, and is particularly concerned with an ophthalmic irrigating solution useful for irrigating the human eye during surgery.

A description of the problems associated with surgical procedures, especially surgical procedures performed on the eye, and the historical development of tissue irrigating solutions may be found in EP-A-0076658.

The stated object of EP-A-0076658 is to provide a stable sterile ophthalmic irrigating solution which, in addition to correct electrolyte balance, provides factors necessary for continued metabolism in the endothelial cells, maintenance of the fluid transport pump system, and consequential maintenance of proper corneal thickness and clarity. This problem is stated to be achieved in EP-A-0076658 by providing a two-part solution system which includes a basic solution and an acidic solution which are individually stable and which, on mixing, form an ocular solution which contains the necessary factors to maintain endothelial cell integrity and corneal thickness during ocular surgery. The combined solution contains the necessary ions in a bicarbonate-phosphate buffer as well as oxidised glutathione and dextrose (d-glucose), the latter being present as an energy source.

There are problems associated with the solution system of EP-A-0076658. Firstly, such a system is relatively expensive because two separate solutions must be prepared and separately sterilised; this problem is not easy to overcome because certain of the ingredients of the system, particularly the oxidised glutathione and the glucose, are heat-labile and cannot therefore be sterilised by an autoclaving procedure as required by various regulatory authorities for

solutions exceeding about 500ml in volume which are to be used in surgical procedures. As a consequence, the two-part system of EP-A-0076658 is prepared, in practice, such that the non-labile components are present in the solution which contains the majority of the fluid which will form the final ocular solution, which is then bottled and autoclaved. The labile components are contained in the other solution of relatively small volume (below the threshold above which autoclaving is required) which may be sterilised by a filtration technique.

A second problem with the solution system of EP-A-0076658 is that its two-part nature can potentially lead to errors in forming the final ocular solution, a procedure which is normally conducted in a hospital.

HEPES has been proposed, in the 1980 article "Intraocular irrigating and replacement fluid", M.V. Graham et al, Trans. Ophthal. Soc. U.K. (1980) 100, p282-285, as a buffer for an intraocular irrigating solution. However, the 1983 article, "A Comparison of HEPES and Bicarbonate Buffered Intraocular Irrigating Solutions: Effects on Endothelial Function in Human and Rabbit Corneas", by Dayle H. Geroski et al, J. Toxicol - Cut & Ocular Toxicol 1(4), 299-309, (1982-83) concludes that HEPES is toxic to endothelial Na^+K^+ATPase and questions the prudence of using HEPES buffer in intraocular irrigating solutions.

It would be an advantage to provide a stable ophthalmic irrigating solution as a single solution capable of being sterilised by autoclaving.

It has now been found that a solution which is effective as an ophthalmic irrigating solution can be formed which does not require the glutathione ingredient previously believed to be essential, but does include a specific buffer to ensure that the

proper pH is maintained prior to and during use.

Thus, according to a first aspect of the present invention there is provided an ocular irrigating solution for irrigating the eye during surgery comprising, a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0.

The organic buffer preferably maintains the solution at a pH in the range 7.2 to 7.8 to match the physiological pH of 7.4.

Highly preferred as the organic buffer are the zwitterionic amino acids, such as N-2-[hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid], commonly referred to as HEPES, which has a pKa of 7.55 at 25°C. Other organic buffers in this family are N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid (BES), pKa=7.1; 3-[N-morpholino]propanesulfonic acid (MOPS), pKa=7.2 at 25°C; N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid (TES), pKa=7.4 at 25°C; N-[2-hydroxyethyl]-piperazine-N'-[3-propanesulfonic acid] (EPPS), pKa=8.0 at 25°C; N-tris[hydroxymethyl]methyl-glycine (TRICINE), pKa=8.1 at 25°C.

The organic buffer should be present in the solution in an amount sufficient to buffer the solution over the duration of the surgical procedure. In practice, this means that the concentration of the buffer should be about 10 to 50 mmol/l.

The bicarbonate source is normally sodium bicarbonate. The bicarbonate source is preferably present in the solution to give a bicarbonate concentration of about 10 to 50 mmol/l, preferably from 15 to 25 mmol/ml to maintain the fluid pump system in the endothelium of the eye.

The ocular irrigating solutions of the present invention are preferably free from glutathione, which

has previously been considered essential for effective performance.

Hitherto it has been considered essential for ocular irrigating solutions to contain an energy source which is purportedly required as a substrate for the various metabolic pathways taking place in the cornea. It has now surprisingly been discovered that ocular irrigating solutions which are free from an energy source (such as glucose) are capable of supporting endothelial function and maintaining corneal thickness as well as solutions containing the energy source. Thus, irrigation solutions of the invention need not contain an energy source. This is of particular significance so far as glucose is concerned which tends to degrade at physiological pH over extended time periods. Therefore, preferred ocular irrigation solutions of the present invention do not contain glucose, or any other energy source which tends to degrade at physiological pH over extended time periods. If an energy source is to be present in an irrigation solution of the invention, a typical concentration is 2-10 mmol/l.

The solution of the invention preferably also contains other electrolytes necessary to maintain physiological function, such as Na^+, K^+, Ca^{2+}, and Cl^-, but not Mg^{2+}, which can lead to the formation of magnesium precipitates in some circumstances. These should be present at concentrations which will permit continued cellular integrity and metabolism. Typically, these electrolytes are present in the following concentrations:

Na^+	130 - 180 mmol/l
K^+	3 - 10 mmol/l
Ca^{2+}	up to 5 mmol/l
Cl^-	130 - 210 mmol/l

Preferably the concentration of Ca^{2+} is at least 0.05 mmol/l, and preferably no more than 0.1 mmol/l.

Moreover, the osmolality should be between approximately 250 - 350 mosmol/kg, preferably 290 - 320 mosmol/kg, to maintain osmotic stability of the cells.

Also normally present in the solution will be a source of phosphate ions, although primarily not for buffering purposes, as in EP-A-00766598, but for normal physiological function. The approximate concentration of phosphate in the solution is normally about 1 mmol/l.

The solution of the invention may be prepared by mixing the components together in aqueous solution, in the desired proportions. It may then be bottled and autoclaved in the normal manner.

One advantage of the invention is that it may be autoclaved without any deleterious effect. For this reason, components which would degrade to a significant extent under the chosen autoclave conditions should be excluded or reduced in amount to a point at which degradation is minimal. Typical autoclave conditions are 121°C for 15 minutes or 134°C for 3 min.

The ocular solution of the invention should preferably be free from nutrients of the type normally present in tissue culture media, namely: amino acids, vitamins, hormones, proteins, growth factors, lipids, nucleosides, minerals.

The solution of the invention may be used in a method of surgery performed on the human eye to replace fluid loss during the operation and to maintain corneal function. Thus according to another aspect of the invention, there is provided an aqueous solution, comprising a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0, for use in a surgical

method, preferably a surgical method performed on the eye.

The invention will now be illustrated by reference to the following Example and drawings in which:

Figure 1A shows the change in corneal thickness during assessment perfusion following 90 minutes exposure to the "UB-M2" solution in accordance with the invention and "BSS Plus";

Figure 1B shows the change in corneal thickness during perfusion with a solution in accordance with the invention "UB-M2" solution and with "BSS Plus".

Example 1

A prior art irrigating solution and an irrigating solution in accordance with the invention were tested in a masked laboratory experiment to evaluate their effectiveness. BSS Plus (which is in accordance with EP-A-0076658) was obtained as a two part system and made up as directed. The composition of these solutions along with those of aqueous humour and BSS are shown in Table 1.

Table 1

	Aqueous humour	BSS	BSS Plus	Invention
Na^+ (mM)	162.9	144.0	160.0	137.2
K^+ (mM)	2.2-3.9	10.0	5.0	5.4
Ca^{2+} (mM)	1.8	4.3	1.0	0.075
Mg^{2+} (mM)	1.1	3.2	1.0	-
Cl^- (mM)	131.6	127.2	130.0	121.2
HCO_3^- (mM)	20.2	-	25.0	20.0
HPO_4^{2-} (mM)	0.6	-	3.0	0.8
SO_4^{2-} (mM)	-	-	-	-
Acetate (mM)	-	28.6	-	-
Citrate (mM)	-	5.8	-	-
Lactate (mM)	2.5-4.5	-	-	-
Glucose (mM)	2.7-3.7	-	5.0	-
Glutathione	1.9 μM	-	0.3 mM	-
HEPES (mM)	-	-	-	20.0
Osmolality (mosmol/kg)	304	302	305	320
pH (20°C)	7.4	7.3	7.4	7.4

Corneas obtained from New Zealand White rabbits (3-4 kg) after an intravenous overdose of pentobarbitone sodium were secured on support rings and perfused as described in J. Physiol 1972; 221: 29-41, "The metabolic basis to the fluid pump in the cornea", Dikstein S. and Maurice DM. The paired corneas from each rabbit were randomly allocated, one to BSS Plus and one to the invention. The allocation was unknown to the person performing the experiment. The epithelial surface was covered with silicone oil to prevent changes in corneal thickness owing to evaporation.

The endothelial surface was perfused at 2.5 ml/h, a pressure of 15 cm H_2O and 35°C. During the first 90 minutes of perfusion, corneas were exposed to the intraocular irrigation solution. This was followed by a further 6 hours of perfusion during which endothelial

function was assessed.

Corneal thickness was measured with an ultrasonic pachymeter (DGH Technologies, Inc), every 30 minutes. The silicone oil was removed briefly to allow the measurements to be made. Each measurement was the mean of readings taken at four different sites of the central cornea.

Changes in corneal thickness during perfusion for 90 minutes with the irrigation solutions are shown in Figure 1A.

Corneal hydration and, thus, thickness are controlled by the endothelium through a pump leak mechanism. Removal of bicarbonate ions from the perfusate suppresses endothelial pump function and causes corneal swelling, although inhibition of the pump is not complete unless CO_2 is also removed from the perfusate. Pump function can be restored and the swelling reversed by returning bicarbonate to the perfusate.

After the 90 minute perfusion with one of the irrigation solutions, endothelial function was, therefore, assessed during a further 6 hours of perfusion with Tissue Culture Medium 199 (TC199). The first 2 hours of perfusion were with TC199 with Earle's salts (Sigma, M3769). This solution contained sodium bicarbonate (26 mmol/l), and should have supported endothelial pump function. Two hours of perfusion with TC199 with Hanks' salts (Sigma, M3274) then followed. This solution did not contain bicarbonate ions and, thus, should have caused corneal swelling, although the solution was not CO_2 free. For the final 2 hours, perfusion with TC199 Earle's was restored and, providing that the endothelium was undamaged, corneas should have thinned. Neither of the TC199 solutions contained phenol red, and their measured osmolalities (Roebling osmometer) were 290 and 288 mosmol/kg,

respectively, for TC199 with Earle's salts and TC199 with Hanks' salts.

Rates of change in corneal thickness both during perfusion with the irrigation solutions and during the three parts of the assessment perfusion were determined by regression analysis. Comparisons were made between groups by t-tests at the 5% level of significance. The results obtained are shown in Table 2 and are also illustrated graphically in Figure 1A.

Table 2

Irrigation solution[a]	Initial 90 min exposure to irrigation solution	Rate of change in corneal thickness (μm/h)[b] TC199 Earle's 0-2 h	TC199 Hank's[c] 2-4 h	TC199 Earle's 4-6 h
BSS Plus	-5.1(4.3)	+0.02(4.2)	+16.1(1.9)	-13.1(5.3)
Invention	-8.4(3.5)	+1.4 (4.7)	+17.7(2.0)	-13.4(3.7)

[a]Corneas were perfused for 90 minutes with an irrigation solution before the assessment perfusion with TC199.

[b]regression coefficient (SD), n=4: + indicates swelling, - indicates thinning.

[c]TC199 Hanks' does not contain HCO_3^-.

There were no differences at the 5% level of significance in rates of change in thickness between corneas exposed to BSS Plus and those exposed to the irrigating solution in accordance with the invention at any stage of the perfusion.

Example 2

An ocular irrigating solution in accordance with the invention was made up as in Example 1.

Corneas were dissected, mounted on support rings and perfused as in Example 1 except that the corneas were perfused continuously for a period of 7.5 hours with either BSS Plus or the invention. Paired corneas, from a single rabbit, were perfused, one with BSS Plus and the other with the invention. The allocation of

corneas to each solution was randomized and masked from the person performing the perfusion. Regression analysis showed no overall change (at the 5% level of significance) in thickness during the course of the perfusion nor was corneal thickness influenced by the type of irrigation solution (see Figure 1B).

In conclusion, Examples 1 and 2 demonstrate that the invention supports endothelial function at least as well as BSS Plus, despite the absence of components, such as glucose and glutathione, that are considered essential constituents of BSS Plus.

CLAIMS

1. An ocular irrigating solution for irrigating the eye during surgery comprising, a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0.

2. An ocular irrigating solution according to claim 1, wherein the organic buffer maintains the solution at a pH in the range 7.2 to 7.8.

3. An ocular irrigating solution according to claim 1 or 2, wherein the organic buffer is a zwitterionic amino acid.

4. An ocular irrigating solution according to claim 3, wherein the organic buffer is N-2-[hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid].

5. An ocular irrigating solution according to any preceding claim, wherein the concentration of the buffer is from 10 to 50 mmol/l.

6. An ocular irrigating solution according to any preceding claim, wherein the bicarbonate source is sodium bicarbonate.

7. An ocular irrigating solution according to claim 6, wherein the bicarbonate source is preferably present in the solution to give a bicarbonate concentration of about 10 to 50 mmol/l.

8. An ocular irrigating solution according to any preceding claim which does not contain glucose, or any other energy source which tends to degrade at physiological pH over extended time periods.

9. An ocular irrigating solution according to any preceding claim having been sterilised by an autoclaving procedure.

10. An ocular irrigating solution according to claim 1, for use in a surgical method performed on the eye.

11. A method of surgery performed on the human eye in which an ocular irrigating solution according to any one of claims 1 to 9 is employed to replace fluid loss during the operation and to maintain corneal function.

12. An ocular irrigating solution substantially as hereinbefore described, with reference to the accompanying examples.

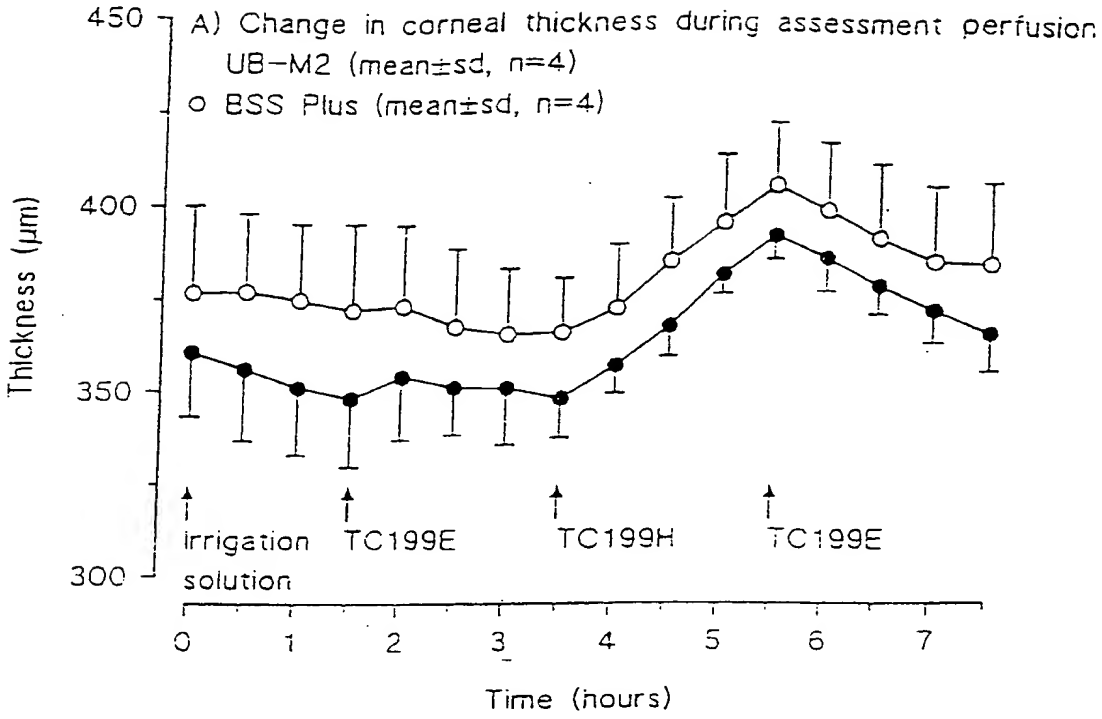

Figure 1A

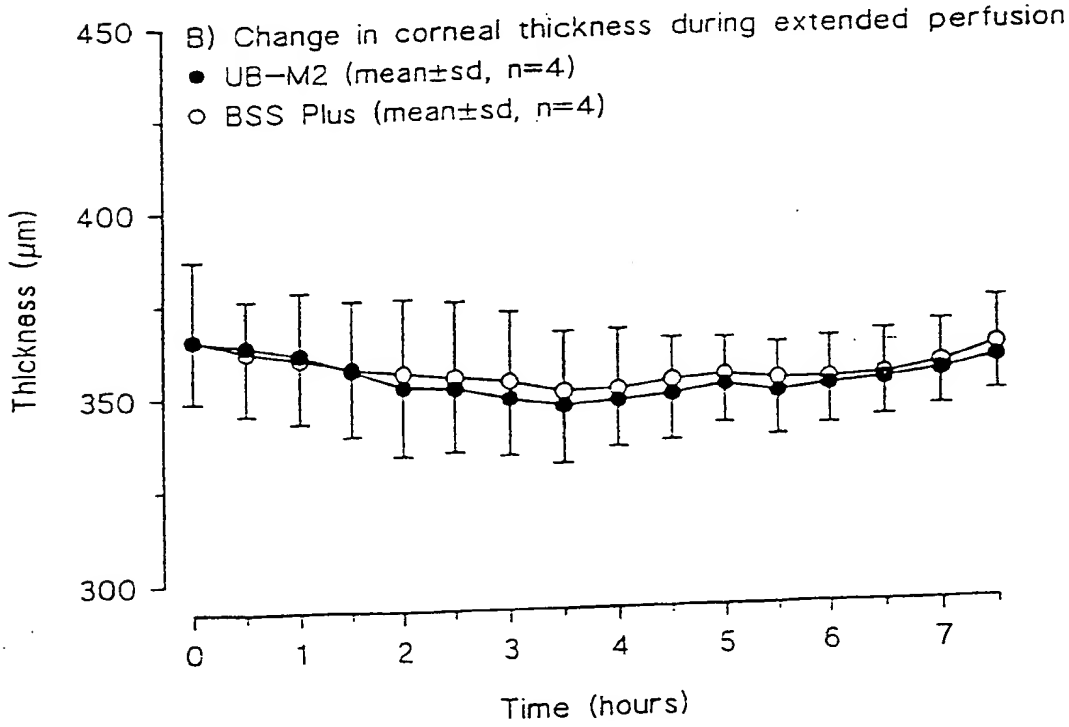

Figure 1B

INTERNAT AL SEARCH REPORT

In [redacted]al Application No
PCT/GB 99/01066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 725 586 A (LINDSTROM ET AL.) 16 February 1988 (1988-02-16) column 1, line 10 - line 30 column 3, line 18 - line 36 column 4, line 8 - line 40 ---	1-12
X	EP 0 435 797 A (ANBEN) 3 July 1991 (1991-07-03) the whole document ---	1-3,5-12
X	FR 2 602 677 A (BLOMET) 19 February 1988 (1988-02-19) page 8; examples 2,3 ---	1-3
A	EP 0 778 021 A (TAISHO PHARMACEUTICAL CO. LTD) 11 June 1997 (1997-06-11) the whole document --- -/--	1-3,5-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 064 320 A (WELSH NATIONAL SCHOOL OF MEDICINE) 17 June 1981 (1981-06-17) the whole document	1-12
A	DE 196 26 479 A (SCHRAGE) 8 January 1998 (1998-01-08) the whole document	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01066

Box I Observations wher certain claims were found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/01066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4725586 A	16-02-1988	US 4696917 A	29-09-1987
		CA 2042152 A	14-11-1992
		EP 0232377 A	19-08-1987
		GB 2186798 A,B	26-08-1987
		JP 63500720 T	17-03-1988
		WO 8700753 A	12-02-1987
		US 4886786 A	12-12-1989
EP 435797 A	03-07-1991	FR 2656527 A	05-07-1991
		AT 112674 T	15-10-1994
		DE 69013315 D	17-11-1994
		DE 69013315 T	24-05-1995
		DK 435797 T	16-01-1995
		ES 2063950 T	16-01-1995
		US 5380537 A	10-01-1995
FR 2602677 A	19-02-1988	NONE	
EP 778021 A	11-06-1997	AU 3484895 A	29-03-1996
		CA 2199610 A	21-03-1996
		CN 1160346 A	24-09-1997
		WO 9608244 A	21-03-1996
		JP 8133968 A	28-05-1996
GB 2064320 A	17-06-1981	NONE	
DE 19626479 A	08-01-1998	NONE	